Long-Acting Narcotic Analgesics
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Schedule	Indication(s)
buprenorphine (Belbuca™)[1]	Endo	CIII	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
buprenorphine (Butrans®)[2]	Purdue	CIII	Management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time for which alternative treatment options are inadequate
fentanyl transdermal (Duragesic®)[3]	generic, Janssen	CII	Management of persistent moderate to severe chronic pain in patients who require continuous, around-the-clock opioid analgesia for an extended period of time for pain that can not be managed by lesser means (age > 2 years) for which alternative treatment options are inadequate; for opioid tolerant patients only
hydrocodone extended-release (Hysingla® ER)[4]	Purdue	CII	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
hydrocodone extended-release (Zohydro® ER)[5]	Zogenix/Pernix	CII	
hydromorphone extended-release (Exalgo®)[6]	generic, Mallinckrodt	CII	Management of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time for which alternative treatment options are inadequate
methadone (Dolophine®)[7]	generic, West-Ward	CII	Relief of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time for which alternative treatment options are inadequate; Detoxification and maintenance treatment of narcotic addiction
morphine sulfate controlled-release (MS Contin®)[8]	generic, Purdue	CII	Pain severe enough to require daily, around-the-clock, long-term opioid analgesia for which alternative treatment options are inadequate
morphine sulfate extended-release* (Kadian®)[9]	generic, Actavis	CII	Pain severe enough to require daily, around-the-clock, long-term opioid analgesia for which alternative treatment options are inadequate
morphine sulfate extended-release and naltrexone (Embeda®)[10]	Pfizer	CII	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

FDA-Approved Indications (continued)

Drug	Manufacturer	Schedule	Indication(s)
oxycodone controlled-release (OxyContin®)[11]	generic, Purdue	CII	Moderate to severe pain requiring around-the-clock, continuous opioid analgesia for an extended time for which alternative treatment options are inadequate in adults and in opioid-tolerant pediatrics ≥ 11 years of age (already receiving at least 20 mg oxycodone or equivalent)
oxycodone extended-release (Xtampza ER™)[12]	Collegium	CII	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options in patients 18 years and older are inadequate
oxymorphone extended-release (Opana® ER)[13]	generic, Endo	CII	Moderate to severe pain requiring around-the-clock, continuous opioid analgesia for an extended time for which alternative treatment options are inadequate
tapentadol extended-release (Nucynta® ER)[14]	Janssen	CII	Moderate to severe pain requiring around-the-clock, continuous opioid analgesia for an extended time for which alternative treatment options are inadequate Neuropathic Pain associated with Diabetic Peripheral Neuropathy (DPN) in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
tramadol extended-release (ConZip®)[15]	generic, Vertical	CIV	Moderate to moderately-severe chronic pain requiring around-the-clock treatment for an extended time period
tramadol extended-release (Ultram® ER)[16]	generic, Janssen	CIV	

* Pfizer has discontinued manufacture of Avinza® non-abuse-deterrent extended-release morphine sulfate capsules. Generic products, approved with Avinza as the reference product, are still available.

Ionsys, a fentanyl iontophoretic transdermal system for pain management in hospitalized patients only, will not be addressed in this review.

OVERVIEW

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting.[17] Pain management must be individualized for each of these patients. There are many opioid analgesic products available, differing in specific opioid, dosage form, abuse-deterrent properties, and duration of action. In this review, the terms “narcotic” and “opioid” are used interchangeably.

Data from 2012 demonstrated that approximately 11.2% of adults report daily pain, which is greatly misunderstood. Historically, data have suggested that pain may be undertreated, but newer estimates imply that opioid treatment for pain may be overutilized.[18] An estimated 20% of patients presenting to outpatient providers with noncancer pain or pain-related diagnoses, whether acute or chronic, receive an opioid prescription. Likewise, per capita opioid prescriptions increased by 7.3% from 2007 to 2012.[19] Caregivers’ misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction may be responsible for the historical undertreatment of pain, and some of the more recent increase in

opioid use is thought to be related to prescribers worrying they are undertreating their patients' pain.[20,21] Unfortunately, approximately 165,000 people have died from overdoses related to opioid pain medications in the U.S. from 1999 to 2014.[22] Likewise, the rates of death related to opioid overdoses have also increased in the past decade, leading to the assessment that the U.S. is experiencing an opioid epidemic. Despite this, persistent pain that is uncontrolled may have clinical, psychological, and social consequences; thus, it is critical to weigh the risks and benefits of opioid use and reevaluate patients routinely for appropriate dose, duration, and treatment choice, including both pharmacologic and nonpharmacologic modalities.

Different management techniques are utilized for acute and chronic pain. When properly used, long-acting opioids decrease administration frequency, decrease the incidence of adverse effects, and increase periods of consistent pain control. While definitions vary, chronic pain generally is defined as pain lasting > 3 months or past the time required for normal tissue healing. It has various etiologies, including injury, inflammation, and underlying medical conditions.[23]

Treatment Guidelines

The World Health Organization's (WHO) guidelines for cancer pain management, long recognized as the foundation of cancer pain relief, recommend a 3-stepped approach with consideration for the type of pain and response to therapy.[24] Initial therapy should include non-opioid analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. For moderate to severe pain, opioid analgesics are the treatment of choice. The American Pain Society does not distinguish amongst the available products in their 2009 clinical guidelines for the use of chronic opioid therapy for the treatment of chronic non-cancer pain.[25] Titration of dose and frequency should be individualized to the patient's response and experience of adverse effects.

In 2016, the American Society of Clinical Oncology (ASCO) published guidelines for chronic pain management in adult cancer survivors.[26] For pharmacologic treatment, systemic non-opioid analgesics and adjuvant analgesics are suggested for chronic pain and to improve function. They state that opioids may be used in those who do not respond to more conservative management.

The 2009 evidence review performed by the American Pain Society in conjunction with the American Academy of Pain Medicine did not identify any significant differences in the benefit or harm of extended-release opioids and related products in the treatment of chronic non-cancer pain.[27] There were also no discernible differences in patient populations that made these analgesics more or less likely to meet the needs of certain patient types.

A position statement released by the American Academy of Neurology (AAN) states that the risks of opioids outweigh their benefits for treating chronic non-cancer pain.[28] AAN states that, while opioids may provide short-term pain relief, there is no proof that they maintain pain relief or improve patients' ability to function over long periods of time without a serious risk of overdose, dependence, or addiction.

In 2016, the Centers for Disease Control and Prevention (CDC) released guidelines for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.[29] These guidelines include 12 recommendations: 3 regarding when to initiate or continue opioids for chronic pain; 4 regarding opioid selection, dosage, duration, follow-up, and discontinuation; and 5 regarding assessing risk and addressing harms of opioid abuse. The guidelines prefer nonpharmacologic and nonopioid

pharmacologic therapy for chronic pain, and recommend a full individual assessment, including risk evaluation and realistic treatment goal setting, prior to prescribing opioids for chronic pain. If opioids are deemed appropriate for a patient's chronic pain, they recommend initial treatment with immediate-release opioids instead of extended-release opioids, which should be prescribed at the lowest effective dose. They further specify that doses of ≥ 50 morphine milligram equivalents (MME)/day should prompt reassessment of the individual's benefits and risks and use of ≥ 90 MME/day should be avoided without justification. They state that long-term opioid use often begins with acute pain treatment; thus, opioids for acute pain should be immediate-release, the lowest effective dose, and the quantity should not exceed the expected duration of pain severe enough to require opioids (typically 3 days and with > 7 days rarely needed). They recommend reassessment within 1 to 4 weeks to determine benefits, harms, and appropriate dosing and continued follow up at least every 3 months. At these visits, efforts should be made to optimize other therapies and taper or discontinue opioids as able and as risks outweigh the individual's benefits. In order to decrease risks, the guidelines recommend avoiding concurrent use of benzodiazepines when possible and risk management strategies, such as offering naloxone in high-risk individuals (e.g., history of overdose, history of substance abuse, doses ≥ 50 MME/day, concurrent benzodiazepine use). Likewise, they recommend urine drug testing at baseline and annually and review of state prescription drug monitoring programs (PDMPs) at baseline and every 3 months. Prescribers should also offer treatment for opioid use disorder (e.g., buprenorphine or methadone in combination with behavioral therapies).

FDA Opioid Regulation

Soon after its approval in the United States in 1995, diversion and abuse of tramadol were reported. This led to the addition of warnings regarding the abuse potential of tramadol to the product labeling by the Food and Drug Administration (FDA). Tolerance, dependence, and addiction to tramadol have been demonstrated and abrupt discontinuation of the drug can result in withdrawal symptoms. Effective August 18, 2014, tramadol-containing products were placed into Schedule IV of the Controlled Substance Act.[30]

In 2013, the FDA announced class-wide safety labeling changes and new post-market study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain. The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.[31]

In April 2015, the FDA released guidance to the industry regarding the development of opioid drug products with abuse-deterrent properties to limit the misuse, abuse, and potentially death associated with these products.[32] This guidance states that abuse-deterrent properties discourage abuse but may not fully prevent abuse. Examples of abuse-deterrent properties include physical/chemical barriers to prevent breakdown of the product, agonist/antagonist combinations, added aversive substances, unique drug delivery systems (e.g., depot injections, implants), or new molecular entities or prodrugs with novel effects (e.g., altered receptor binding or require enzymatic activation). In order for the FDA to approve a formulation as an abuse-deterrent formulation, an abuse-deterrent property is not sufficient; the manufacturer should demonstrate that the product deters abuse in studies. The types of studies the FDA requires are laboratory-based *in vitro* manipulation and extraction studies, pharmacokinetic studies, and clinical abuse potential studies, which commonly measures drug-liking by subjects without pain and with

current addiction behaviors. The following agents have demonstrated abuse-deterrence in studies, thus meeting FDA requirements for abuse-deterrent formulations: Embeda capsules, Hysingla ER tablets, OxyContin biconcave tablets, oxycodone ER (authorized generics of Oxycontin) tablets, and Xtampza ER capsules.[33,34,35,36] As a result, the labeling of these products includes information regarding abuse-deterrence, reflecting the FDA's approval of these products as abuse-deterrent formulations.

In February 2016, the FDA announced plans to reassess their approach to opioid medications with a focus on policies to reverse the epidemic of deaths associated with opioid use.[37] Select components of the action plan include the use of an expert advisory committee prior to the approval of an opioid without abuse-deterrent properties, the formation of a Pediatric Advisory Committee who will review pediatric labeling for new products, an update of risk evaluation and mitigation strategy (REMS) requirements and improvement in access to abuse-deterrent formulations, naloxone, and other treatment options for patients with opioid-use disorders.

PHARMACOLOGY[38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54]

Opioid agonists reduce pain by acting primarily through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center. Buprenorphine (Belbuca, Butrans) differs in that it is a partial agonist/antagonist of opioid receptors.

Naltrexone, a component of Embeda, is a centrally-acting mu-receptor antagonist that reverses the analgesic effects of mu-receptor agonists by competing for binding sites with opioids.

Tapentadol (Nucynta ER) is a centrally-acting synthetic analgesic and exerts its analgesic effects without a pharmacologically active metabolite. The exact mechanism of action is unknown. Tapentadol also inhibits norepinephrine reuptake.

In addition to binding to the mu-opioid receptors, tramadol (Conzip, Ultram ER) exerts its effect through weak inhibition of norepinephrine and serotonin reuptake.

PHARMACOKINETICS[55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71]

Drug	Half-Life (hr)	Tmax (hr)	Excretion
buprenorphine (Belbuca)	27.6	3	69% metabolized and eliminated in feces and approximately 30% excreted in urine
buprenorphine (Butrans)	26	about 48-72	70% metabolized and eliminated in feces and approximately 27% excreted in urine
fentanyl transdermal (Duragesic)	3–12	28.8–35.8	75% metabolized and renally eliminated
hydrocodone ER (Hysingla ER)	7–9	14–16	primarily metabolized and renally eliminated
hydrocodone ER (Zohydro ER)	8	5	highly metabolized; 26% eliminated in urine
hydromorphone ER (Exalgo)	8–15	12–16	highly metabolized; 75% eliminated in urine
methadone (Dolophine)	8–59	1–7.5	highly metabolized; eliminated in urine and feces
morphine sulfate CR (MS Contin)	2–15	~ 1.5	90% metabolized and renally eliminated
morphine sulfate ER (Kadian)	2–15	8.6–10.3	90% metabolized and renally eliminated
morphine sulfate ER / naltrexone (Embeda)	29	7.5	90% metabolized and renally eliminated
oxycodone CR (OxyContin)	4.5	1.6–3.2	primarily metabolized and renally eliminated
oxycodone ER (Xtampza ER)	4–4.5	~5.6	primarily metabolized and renally eliminated
oxymorphone ER (Opana ER)	9.4–11.3	1–2	highly metabolized; eliminated in urine and feces
tapentadol ER (Nucynta ER)	5	3–6	97% metabolized and renally eliminated
tramadol ER (ConZip)	tramadol 10 metabolites 11	tramadol 5.9 metabolites 11	30% excreted as tramadol, 60% excreted as active metabolites in the urine
tramadol ER (Ultram ER)	tramadol 7.9 metabolites 8.8	tramadol 12 metabolites 15	30% excreted as tramadol, 60% excreted as active metabolites in the urine

nr = not reported

CONTRAINDICATIONS/WARNINGS[72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88]

Contraindications

The agents in this review are contraindicated in patients with a known hypersensitivity to any component of the product. Hydromorphone (Exalgo) is also contraindicated in patients with known hypersensitivity to sulfites. Oxymorphone ER (Opana ER) is contraindicated in patients with a known hypersensitivity to morphine analogs, such as codeine.

Long-acting opioids are contraindicated in patients who are not opioid-tolerant; patients who have acute or severe bronchial asthma; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus.

In general, long-acting opioids are not indicated as an as-needed analgesic; for example, for use in the management of acute pain, mild pain, or intermittent pain, or in patients who require opioid analgesia

for a short period of time in the management of post-operative pain, including use after outpatient or day surgeries (e.g., tonsillectomies).

Oxymorphone ER is contraindicated in patients with moderate and severe hepatic impairment.

Tapentadol ER (Nucynta ER) is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events.

Tramadol ER (Ultram ER and ConZip) is contraindicated in patients who have acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs, and situations where opioids may be contraindicated.

Warnings

Boxed Warnings

Buprenorphine transdermal (Belbuca, Butrans), methadone (Dolophine), fentanyl transdermal (Duragesic), morphine sulfate ER/SR (Kadian, MS Contin), morphine sulfate ER/naltrexone (Embeda), hydrocodone ER (Hysingla ER, Zohydro ER), hydromorphone ER (Exalgo), morphine sulfate controlled-release (MS Contin), oxymorphone ER (Opana ER), oxycodone CR (OxyContin), oxycodone ER (Xtampza ER), and tapentadol ER (Nucynta ER) boxed warnings include: monitoring for signs of misuse, abuse, and addiction during therapy; fatal respiratory depression may occur, with the highest risk at initiation and with dose increases; and accidental exposure can result in the fatal overdose of the above medications in children. Although not boxed, tramadol ER (Conzip, Ultram ER) labeling contains similar warnings.

The boxed warning for methadone (Dolophine) indicates that cardiac and respiratory deaths have been reported during initiation and conversion of pain patients to methadone treatment from other opioid agonists. Cases of QT interval prolongation and serious arrhythmia have also been observed.

Chronic maternal use of opioids during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome; infants may require treatment if exposed to opioids during gestation.

Respiratory depression is the chief hazard of opioid agonists. Serious or life-threatening hypoventilation may occur at any time during the use of long-acting opioids, especially during the initial 24 to 72 hours following initiation of therapy and following increases in dose. Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non-tolerant patients or when opioids are given in conjunction with other agents that depress respiration, such as alcohol and other central nervous system depressants. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

When the patient no longer requires therapy with agents in this class, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

In August 2016, the FDA issued a Drug Safety Communication regarding the risk of death when combining opioid pain medications or cough medicine with benzodiazepines and other central nervous system depressants. The FDA is requiring an additional boxed warning for all opioids describing this risk. They

state that medications should only be used together when other treatment alternatives are inadequate, and the lowest dose should be used for the shortest duration. Also, patients should be advised of the adverse effect risks and signs and symptoms of respiratory depression and sedation.[89]

Patients should not to consume alcohol or any products containing alcohol while taking morphine sulfate ER/naltrexone (Embeda) because co-ingestion can result in fatal plasma morphine levels.

Oxycodone CR and ER (Oxycontin, Xtampza ER) also carries a boxed warning for drug interactions associated with cytochrome P450 3A4 inhibitor or inducer initiation or discontinuation potentially altering drug exposure which, could lead to overdose.

Other Warnings

Long-acting opioids may worsen increased intracranial pressure and obscure its signs. Patients at increased risk of hypotension and those in circulatory shock could experience worsened conditions with treatment. Orthostatic hypotension and syncope have also been reported with opioids. Patients at higher risk of hypotension include those with hypovolemia or those taking concurrent products that compromise vasomotor tone (e.g., phenothiazines, general anesthetics).

All agents in this review, except tramadol ER, may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsened symptoms.

All opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug (e.g., monoamine oxidase [MAO] inhibitors, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRI], tricyclic antidepressants [TCAs], triptans, linezolid, or lithium). Serotonin syndrome typically occurs within several hours to a few days following use.[90]

Monitor patients with a history of seizure disorders for worsened seizure control during therapy with buprenorphine, hydromorphone ER, morphine ER/CR, morphine ER/naltrexone, oxycodone CR, oxymorphone ER, tapentadol ER, and tramadol ER since these agents can aggravate seizure disorder and may induce seizures in some clinical settings. This is not reported for fentanyl transdermal or hydrocodone ER medications.

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH) and cortisol. All opioids carry a warning for adrenal insufficiency; if an opioid causes adrenal insufficiency, treat with corticosteroids and withdraw the opiate as appropriate.[91]

Initiation of concurrent therapy with CYP3A4 inhibitors, or discontinuation of CYP3A4 inducers with buprenorphine, fentanyl transdermal, hydrocodone ER, and oxycodone CR/ER, can result in a fatal opioid overdose.

All tablets or capsules of oral long-acting opioids should be swallowed whole. Taking broken, chewed, or crushed tablets or capsules can lead to a rapid release and absorption of a potentially fatal dose of the drug.

Buprenorphine and fentanyl patches are for transdermal use on intact skin only. Avoid exposure to direct heat while wearing the patch because an increased absorption of the drug can occur. Monitor patients who develop increased body temperature for opioid side effects and adjust dose if signs of respiratory or central nervous system depression is seen. Buprenorphine patches should not be used if the pouch

seal is broken or the patch is cut, damaged, or changed in any way. Damaged or cut fentanyl patches should not be used.

Use of opioids with other CNS depressants may result in hypotension, sedation, respiratory depression, coma, or death.

Due to the risk of sedation with opioids, this may impair a patient's ability to drive or operate heavy machinery.

If urine testing for clinical management is needed, the assay should be assessed to ensure the sensitivity and specificity are appropriate.

buprenorphine buccal (Belbuca) and buprenorphine transdermal (Butrans)

Avoid using buprenorphine in patients with long QT syndrome or a family history of the disease. Use caution in patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease. These patients should not exceed a dose of one 20 mcg/hr buprenorphine transdermal patch due to the risk of QTc prolongation.

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence. For patients with an increased risk of hepatotoxicity (e.g., history of excessive alcohol intake, liver disease), monitor liver enzyme levels before and periodically during treatment with buprenorphine. The risk of overdose may be greater in patients with moderate to severe hepatic impairment.

Cancer patients with oral mucositis may absorb buprenorphine buccal (Belbuca) more quickly than intended. A dose reduction is recommended in patients with known or suspected mucositis.

Rare cases of severe application site skin reactions have been reported with use of buprenorphine transdermal patches. Onset can occur within days to months after treatment starts. Discontinue therapy if this occurs.

Buprenorphine transdermal has not been studied for use in the management of addictive disorders.

fentanyl transdermal (Duragesic)

In 2005 and again in 2007, the FDA issued safety communications that highlight important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch).[92] However, the FDA continues to receive reports of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat source. Directions for prescribing and using the fentanyl patch must be followed exactly to prevent death or other serious side effects from fentanyl overdose.

Fentanyl may cause bradycardia; monitor patients with bradyarrhythmias.

hydrocodone bitartrate ER (Zohydro ER/Hysingla ER)

QTc prolongation has been observed with daily doses of hydrocodone ER 160 mg and should be considered when prescribing this agent in patients with congestive heart failure, bradyarrhythmias, electrolyte imbalances, or who are taking medications known to cause QTc prolongation. Avoid hydrocodone ER in patients with congenital long QT syndrome. A dose reduction or a change to an alternative analgesic should be made in patients who develop QTc prolongation.

Alcohol or alcohol-containing products should not be consumed while taking hydrocodone bitartrate extended-release as co-ingestion can result in fatal plasma hydrocodone levels.

morphine extended-release/naltrexone (Embeda)

Morphine sulfate ER/naltrexone (Embeda) capsules contain pellets of morphine sulfate with a sequestered core of naltrexone. Tampering with the pellets by crushing or chewing causes rapid release and absorption of both morphine and naltrexone, resulting in a potentially fatal morphine dose, particularly in opioid-naïve individuals. In opioid-tolerant patients, the absorption of naltrexone may increase the risk of precipitating withdrawal. Morphine sulfate ER/naltrexone 100/4 mg capsules are for opioid-tolerant patients. Patients should not consume alcoholic beverages or use prescription or non-prescription medications containing alcohol while on this therapy.

Naltrexone may or may not interfere with enzymatic methods for the detection of opioids in the urine depending on the specificity of the test. Consult the test manufacturer for specific details.

oxycodone CR (OxyContin)

A reformulation of oxycodone CR (OxyContin) was approved in 2010 by the FDA, as well as the first reformulated generic version. These new formulations were designed to decrease the likelihood that this medication will be misused or abused, and result in overdose. The reformulation added tamper-resistant features aimed at preserving the controlled release of the active ingredient, oxycodone.[93,94] Any attempt to dissolve the tablets in liquid results in a gummy substance. The oxycodone CR 60 mg and 80 mg tablets (or a single dose greater than 40 mg) are to be used in opioid-tolerant patients only, since fatal respiratory depression may occur when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

oxycodone ER (Xtampza ER)

The risk of overdose may be greater in patients with moderate to severe hepatic impairment.

oxymorphone ER (Opana ER)

In October 2012, the FDA issued a safety warning that thrombotic thrombocytopenic purpura appears to occur with the use of oxymorphone ER when it is abused and injected intravenously and kidney failure requiring dialysis, as well as death, has been reported.[95] Oxymorphone ER should only be taken orally.

tramadol extended-release (Ultram ER /ConZip)

Tramadol ER should not be prescribed for patients who are suicidal or addiction-prone. Tramadol extended-release formulations are for oral use only, should be swallowed whole, and should not be chewed, dissolved, split, or crushed.

Risk Evaluation and Mitigation Strategy (REMS)[96,97,98]

Effective July 9, 2012, revised REMS for extended-release (ER) and long-acting (LA) opioid medications was introduced. The FDA communicated that this class contains highly potent medications whose approved indication is to treat moderate-to-severe persistent pain for serious chronic conditions. In addition, misuse and abuse of these medications was addressed referencing a serious public health crisis of addiction, overdose, and death. The REMS introduces new safety measures (including dispensing of medication guides and prescriber training).

Minor changes were made to the extended-release and long-acting opioid REMS program in October 2015, including revised titration information for methadone tablets. Other minor changes to the shared REMS program have also occurred over the years. The current requirements of the ER/LA opioids REMS program include a medication guideline and healthcare provider training, including prescriber letters, blueprints for education points, patient counseling documents, and organization and licensing board education letters.

DRUG INTERACTIONS[99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115]

All long-acting narcotics should be used with caution and in reduced doses in patients who are concurrently receiving other narcotic analgesics, muscle relaxants, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, tricyclic antidepressants, or other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Mixed agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, butorphanol) and partial agonists (buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic, including morphine ER/naltrexone (Embeda). In these patients, the mixed agonist/antagonist or partial agonist may alter the analgesic effect or may precipitate withdrawal symptoms.

Monoamine oxidase inhibitors (MAOIs) may intensify the actions of fentanyl transdermal, hydrocodone ER, hydromorphone ER, morphine CR/ER, morphine/naltrexone, tapentadol ER, and tramadol ER; these long-acting opioids should not be taken in patients taking MAOIs or within 14 days of stopping MAOI treatment.

All opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug as described above.[116]

Concomitant use of diuretics and anticholinergics with opioids may reduce the efficacy of the diuretic and increase the risk of urinary retention respectively; monitor and adjust the doses as needed.

Drugs that induce or inhibit cytochrome P450 3A4 enzymes may affect the metabolism of buprenorphine, fentanyl transdermal, hydrocodone ER, oxycodone CR/ER, and tramadol ER. Initiation of concurrent therapy with CYP3A4 inhibitors, or discontinuation of CYP3A4 inducers with these agents, can increase the risk of serious adverse events. However, co-administration of the strong CYP3A4 inhibitor ketoconazole 200 mg with buprenorphine transdermal 10 mcg/hr did not result in changes in the buprenorphine pharmacokinetic profile. Concurrent use of a CYP3A4 inducer may result in a reduced analgesic effect.

Tramadol is metabolized by CYP2D6 to form an active metabolite. Concomitant administration of CYP2D6 inhibitors, such as quinidine, fluoxetine, paroxetine, and amitriptyline, may reduce metabolic

clearance of tramadol increasing the risk for serious adverse events including seizures. Drugs that induce or inhibit cytochrome P450 3A4 enzymes may affect the metabolism oxycodone CR/ER; monitor and adjust dosage as required if concomitant use is warranted.

The use of buprenorphine, fentanyl transdermal, hydrocodone ER, hydromorphone ER, morphine CR/ER, morphine ER/naltrexone, oxycodone CR, oxymorphone ER, or tapentadol ER with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. P-glycoprotein (P-gp) inhibitors, such as quinidine, may increase the exposure of morphine by 2-fold. Cimetidine can potentiate respiratory depression when given with oxymorphone or morphine. Morphine and oxycodone can reduce the effect of diuretics.

ADVERSE EFFECTS[117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133]

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
buprenorphine (Belbuca)	< 1	4–13 (3)	2–6 (1)	< 1	2–6 (3)	10–50 (7)	< 5	1–7 (< 1)	4–8 (< 1)
buprenorphine (Butrans)	1–5	3–13 (1–5)	2–15 (1–7)	≥ 1– < 5	5–16 (5–11)	13–23 (8–11)	3–9 (6)	2–13 (2–4)	4–9 (1)
fentanyl transdermal (Duragesic)	> 10	> 10	3–10	3–10	3–10	> 10	> 1	> 10	> 10
hydrocodone ER (Hysingla ER)	≥ 1 – < 5	≥ 5	≥ 5	< 1	≥ 5	≥ 5	≥ 1– < 5	≥ 5	≥ 5
hydrocodone ER (Zohydro ER)	nr	8 (0)	2 (1)	1–10 (nr)	0 (1)	7 (3)	1–10 (nr)	1 (0)	7 (1)
hydromorphone ER (Exalgo)	1–4 (4)	7–15 (4)	2–4 (1)	reported	5–8 (7)	9–12 (7)	reported	1–9 (0)	6 (4)
methadone (Dolophine)	reported	reported	reported	reported	reported	reported	reported	reported	reported
morphine sulfate CR (MS Contin)	reported	reported	reported	nr	reported	reported	reported	reported	reported
morphine sulfate ER (Kadian)	2	9	6	3	< 2	7	3	9	2
morphine sulfate ER / naltrexone (Embeda)	reported	31.2	4.1	nr	6.9	22.2	< 1	7.3	8
oxycodone CR (OxyContin)	6 (nr)	23 (7)	13 (9)	1-5	7 (7)	23 (11)	1-5	23 (4)	12 (7)
oxycodone ER (Xtampza ER)	nr	5.2–13 (0.5)	1.6–5.7 (0)	< 1	6.2–13.9 (11.7)	10.9–16.6 (4.6)	1–5	<1–8.8– (< 1)	4.1–6.4 (1.5)
oxymorphone ER (Opana ER)	nr	27.6 (13.2)	17.8 (7.6)	1–10	12.2 (5.6)	33.1 (13.2)	nr	17.2 (2.2)	15.6 (4.1)
tapentadol ER (Nucynta ER)	2 (1)	17 (7)	17 (6)	1 (0)	15 (13)	21 (7)	1 (<1)	12 (4)	8 (3)
tramadol ER (Ultram ER)	3.5–6.5	12.2–29.7	15.9–28.2	1– < 5	11.5–15.8 (10.6)	15.1–26.2	nr	7.3–20.3 (1.7)	5–9.4
tramadol ER (ConZip)	3.5–8.6	9.3–21.3	9.6–13.6	nr	19.0–23.1	16.1–25.1	1-5	11.7–16.1	6.5–10.4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported.

Opioids have been associated with a decrease in sex hormone levels. Laboratory assessment is recommended in patients who report low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.[134]

SPECIAL POPULATIONS[135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151]

Pediatrics

Fentanyl transdermal (Duragesic) is approved for use in patients as young as 2 years of age who are opioid-tolerant. Oxycodone CR (OxyContin) is approved for use in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerating at least 20 mg oxycodone orally (or its equivalent.

Safety and efficacy of buprenorphine transdermal (Butrans), buprenorphine buccal (Belbuca), hydrocodone bitartrate ER (Hysingla ER, Zohydro ER), methadone (Dolophine), morphine sulfate CR/ER (Kadian, MS Contin), morphine sulfate ER/naltrexone (Embeda), oxycodone ER (Xtampza ER), oxymorphone ER (Opana ER), tramadol ER (ConZip, Ultram ER), and tapentadol ER (Nucynta ER) have not been established in patients younger than 18 years of age. Safety and efficacy of hydromorphone ER (Exalgo) has not been established in patients younger than 17 years of age.

While not approved in this population, the FDA is investigating the use of tramadol formulations (Conzip, Ultram ER) in patients < 18 years old due to the rare but serious risk of slowed or difficulty breathing, which may be increased in pediatric patients receiving doses for pain control following tonsillectomy or adenoid surgery.[152] The FDA recommended alternative pain medications in this population.

Geriatrics

Elderly patients may be more sensitive to the opioid agonist effects than younger patients. Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating opioid therapy and when given in conjunction with other drugs that depress respiration.

Administration of oxymorphone ER in elderly patients resulted in plasma levels that were 40% higher than those in younger subjects.

In clinical trials with buprenorphine buccal (Belbuca), adverse effects were higher in elderly patients than in younger adults.

In clinical trials with oxycodone ER (Xtampza ER), oxycodone exposure was higher in elderly patients than in younger adults, but no unexpected or untoward adverse effects occurred. Use cautiously in this population.

Pregnancy

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. Opioids cross the placenta and may produce respiratory depression in neonates. Opioids are not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions.

Buprenorphine transdermal, fentanyl transdermal, hydrocodone ER, hydromorphone ER, morphine sulfate ER products, morphine sulfate ER/naltrexone (Embeda), oxymorphone ER, tramadol ER, and tapentadol ER have a Pregnancy Category C designation.

Methadone also has a Pregnancy Category C designation. Women on high-dose methadone maintenance already nursing should be counseled to wean breast-feeding gradually to prevent neonatal abstinence syndrome.

Oxycodone CR has a Pregnancy Category B designation. While animal studies did not reveal evidence of fetal harm, there are no adequate or well-controlled studies in pregnant women; animal studies are not always predictive of human response. Therefore, oxycodone CR should be used during pregnancy only if clearly required. There are no adequate and well-controlled studies of oxycodone ER (Xtampza ER) in pregnant women.

There are no adequate and well-controlled studies of buccal buprenorphine (Belbuca) in pregnant women.

Hepatic Impairment

Oxymorphone ER is contraindicated in patients with moderate to severe hepatic impairment.

Avoid use of fentanyl transdermal, tapentadol ER, and tramadol ER in patients with severe hepatic impairment. Reduce dose of tapentadol ER in patients with moderate hepatic impairment.

Initiate hydrocodone ER therapy at 50% of the usual starting dose in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression.

Hydromorphone ER should be initiated at 25% of the usual starting dose in patients with moderate hepatic impairment and closely monitor these patients for respiratory and central nervous system depression during initiation and dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied.

Oxycodone CR/ER should be initiated at 33% to 50% of the usual starting dose and carefully titrated in patients with hepatic impairment. An alternative analgesic is recommended in those requiring a dose of < 9 mg.

Buprenorphine transdermal has not been evaluated in patients with severe hepatic impairment. Since it is intended for 7-day dosing, alternate analgesic therapy should be considered in patients with severe hepatic impairment.

The pharmacokinetics of morphine in patients with severe hepatic impairment have not been adequately studied.

Buccal buprenorphine (Belbuca) has not been evaluated in patients with severe hepatic impairment; dosage adjustments are not required for patients with mild to moderate hepatic impairment.

Renal Impairment

Avoid use of fentanyl transdermal, tapentadol ER, and tramadol ER in patients with severe renal impairment.

Use oxycodone CR/ER with caution in patients with renal impairment. In renally impaired patients (estimated creatinine clearance [CrCl] < 60 mL/min), plasma exposure may be 50% higher than in those

with normal renal function. An alternative analgesic is recommended in those requiring a dose of < 9 mg.

Titrate oxymorphone ER slowly in patients with moderate to severe renal impairment.

Although accumulation of morphine metabolites has been found in people with renal failure, adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been performed.

Start hydromorphone ER therapy at 50% of the usual starting dose in patients with moderate renal impairment and 25% of the usual starting dose in patients with severe renal impairment. Closely monitor patients for respiratory and central nervous system depression during initiation and during dose titration. Hydromorphone ER is only intended for once daily administration; consider an alternate analgesic that may provide more dosing flexibility in patients with severe renal impairment.

Initiate therapy with 50% of the initial dose of hydrocodone ER in patients with moderate or severe renal impairment or end-stage renal disease and monitor closely for adverse events such as respiratory depression.

No impact of creatinine clearance on steady state buprenorphine concentrations has been found.

No differences in pharmacokinetics of buccal buprenorphine (Belbuca) were found in patients on dialysis and those with normal renal function.

DOSAGES[153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170]

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
buprenorphine buccal (Belbuca)	75 mcg buccally every 12 to 24 hours, as tolerated	For opioid-naïve patients: 75 mcg buccally every 12 to 24 hours, as tolerated, for at least 4 days prior to increasing to 150 mcg every 12 hours For opioid-experienced patients, there is a dosing conversion chart in the prescribing information; do not initiate until patient has been tapered to an oral morphine sulfate equivalent of 30 mg or less; Maximum dose: 900 mcg every 12 hours	75, 150, 300, 450, 600, 750, and 900 mcg buccal film	No
buprenorphine transdermal (Butrans)	1 patch changed every 7 days	For opioid-naïve patients: Initiate treatment with buprenorphine transdermal 5 mcg/hour and titrate as needed after 72 hours For opioid-experienced patients, there is a dosing conversion chart in the prescribing information; Do not exceed a dose of one 20 mcg/hour patch due to the risk of QTc prolongation	5, 7.5, 10, 15, 20 mcg/hr patches	No
fentanyl transdermal (Duragesic)	25 mcg/hr patch changed every 3 days for opioid-tolerant patients	For patients on other opioids, calculate their total 24-hour analgesic requirement, then convert this amount to an equivalent analgesic oral morphine dose (see Package Insert); Dosage increase may occur after every 3 days by adding up the rescue medication dosage; Initial doses should be reduced in elderly or debilitated patients	12, 25, 37.5, 50, 62.5, 75, 87.5, 100 mcg/hr patches	No
hydrocodone ER (Zohydro ER)	10 mg every 12 hours	Adjust dosage in increments of 10 mg every 12 hours every 3 to 7 days until adequate pain relief with minimal adverse reactions is achieved; refer to the package insert for conversion factors For opioid-tolerant patients, use the conversion chart to calculate the approximate hydrocodone daily dose and then divide in half for administration every 12 hours; always round down, if necessary, to the appropriate hydrocodone ER strengths available	10, 15, 20, 30, 40, 50 mg capsules[†] (Viscous gel develops if crushed and dissolved in liquids or solvents)	No
hydrocodone ER (Hysingla ER)	20 mg orally every 24 hours	Adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days, as needed, to achieve adequate analgesia	20, 30, 40, 60, 80, 100, 120 mg tablets	Yes (Formulation deters misuse and abuse via chewing, snorting, or injection)

Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
hydromorphone ER (Exalgo)	8 to 64 mg once daily	Adjust dosage not more often than every 3 to 4 days; individually titrate dosing to allow pain control while minimizing adverse reactions	8, 12, 16, 32 mg tablets (Uses Osmotic extended-Release Oral delivery System or OROS, making it difficult to crush or extract for injection)	No
methadone (Dolophine)	2.5 mg to 10 mg every 8 to 12 hours	Adjust dosage according to the severity of pain and patient response; for exceptionally severe pain, or in those tolerant of opioid analgesia, it may be necessary to exceed the usual recommended dosage	5, 10, 40 mg tablets 1, 2, 10 mg/mL oral solutions	No
morphine sulfate ER (Kadian)	1 capsule every 12 to 24 hours based on previous opioid requirements	Titrate to pain control; do not exceed upward titration of more than 20 mg every other day Swallow capsules whole; do not crush, chew, or dissolve capsules or contents of capsules; may sprinkle pellets on applesauce The 100 mg, 130 mg, 150 mg, and 200 mg capsules should only be used in opioid-tolerant patients	10, 20, 30, 50, 60, 80, 100, 200 mg capsules‡ 30, 45, 60, 75, 90, 120 mg capsules§	No
morphine sulfate CR (MS Contin)	15 mg every 12 hours	In adjusting dosing regimens, attention should be given to daily dose, degree of opioid tolerance, if any, and general condition and mental status of the patient Do not crush, chew, break, or dissolve tablets The 100 mg and 200 mg tablets should only be used in opioid-tolerant patients	15, 30, 60, 100, 200 mg tablets	No
morphine sulfate ER/naltrexone (Embeda)	1 capsule every 12 to 24 hours	Titrate to pain control; initiate therapy at the lowest dose for patients who use Embeda as their first opioid analgesic For patients who are converting from another oral morphine product, therapy should begin with half of the total established daily morphine dose being given twice daily, or with the full dose being given once a day Swallow capsules whole or may sprinkle on applesauce; do not crush, chew, or dissolve capsules or contents of capsules The 100/4 mg capsules are reserved for opioid-tolerant patients	20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, 100/4 mg capsules	Yes (Features a sequestered core of naltrexone to deter crushing, chewing, or dissolving)

Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
oxycodone CR (OxyContin)	10 mg every 12 hours	Except for the increase from 10 mg to 20 mg every 12 hours, the total daily oxycodone CR dose can be increased by 25 to 50% at each increase; patients should be titrated so that they need no more than 2 supplemental analgesia doses per day; a conversion chart is found in the package insert for patients on other opioid therapy For elderly, debilitated, and patients with hepatic impairment, the dosage should be reduced by 33% to 50% For patients with creatinine clearance < 60 mL/min, dosage may need to be lowered by up to 50% Pediatric dosing is similar to adult dosing Single doses greater than 40 mg or total dose greater than 80 mg should only be used in opioid-tolerant patients	10, 15, 20, 30, 40, 60, 80 mg tablets	Yes (Reformulated to diminish the ease of cutting, breaking, chewing, crushing, or dissolving and to form viscous gel when mixed with aqueous liquid)
oxycodone (Xtampza ER)	9 mg orally every 12 hours taken with food (may sprinkle capsule contents onto food or in a cup for administration by mouth, nasogastric tube, or gastronomy tube)	Adjustments in dosing are recommended to occur no earlier then every 1 to 2 days Single doses of ≥ 36 mg and total daily doses of ≥ 72 mg should be reserved for patients whom have shown tolerance for comparable opioid potency analgesia Maximum daily dose is 288 mg (320 mg oxycodone HCl per day)	9, 13.5, 18, 37, and 36 mg capsules	Yes (Employs DETERx® technology: a microsphere-in-capsule formulation; in each microsphere, oxycodone is present as a solid solution of a fatty acid salt (oxycodone myristate) in a hydrophobic matrix that also contains waxes)[171]
oxymorphone ER (Opana ER)	5 mg every 12 hours	Increase by 5 to 10 mg twice a day every 3 to 7 days based on patient pain intensity and adverse effects Do not attempt to break, crush, chew, or dissolve tablets In patients with creatinine clearance < 50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly while carefully monitoring adverse effects	5, 7.5, 10, 15, 20, 30, 40 mg biconcave tablets (Formulation resistant to crushing and dissolution-forms viscous gel to trap active agents)	No

Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
tapentadol ER (Nucynta ER)	50 mg every 12 hours	Titrate to pain control within therapeutic range of 100 to 250 mg twice a day; in patients previously taking other opioid therapy, initiate with 50 mg then titrate to effective and tolerable dose within range of 100 to 250 mg twice a day; titrate dose by no more than 50 mg/dose twice a day (100 mg/day) no more than every 3 days Do not exceed maximum daily dose of 500 mg (250 mg twice a day)	50, 100, 150, 200, 250 mg tablets (Resistant to breaking or crushing)	No
tramadol ER (ConZip)	100 mg daily	Initiate at 100 mg daily then titrate at 100 mg increments every 5 days as needed to relieve pain, up to max 300 mg/day; dose no more frequently than every 24 hours For patients maintained on tramadol immediate-release tablets, calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release capsules rounded down to the next lowest 100 mg increment; individualize dose as needed, up to a max 300 mg/day Consider lower doses in elderly The concomitant use of the extended-release capsules with other tramadol products is not recommended	100, 150, 200, 300 mg capsules	No
tramadol ER (Ultram ER)	1 tablet daily	Initiate at 100 mg daily then titrate at 100 mg increments every 5 days as needed to relieve pain, up to a max of 300 mg/day; do not use in patients with severe renal or hepatic impairment	100, 200, 300 mg tablets	No

* Has met requirements by the FDA to be approved as an abuse-deterrent formulation.

† Reformulated Zohydro ER with abuse-deterrent properties is available; originally-marketed formulations are no longer available.

‡ The morphine sulfate ER (Kadian) 130 mg and 150 mg formulations have been discontinued.

§ Select strengths are generics for Avinza (morphine sulfate extended-release), which is no longer marketed.

The following medications are available as abuse-deterrent formulations: morphine sulfate ER/naltrexone (Embeda) capsules; hydrocodone ER (Hysingla ER) tablets; oxycodone CR (OxyContin) tablets); oxycodone ER (authorized generics for Oxycontin) tablets; and oxycodone ER capsules (Xtampza ER). Although hydromorphone ER (Exalgo), oxymorphone ER (Opana ER), tapentadol ER (Nucynta ER), and hydrocodone ER (Zohydro ER) have abuse-deterrent properties they have not been approved by the FDA as abuse-deterrent formulations.

Due to significant pharmacokinetic variability among patients, close observation and slow titration of methadone (Dolophine) is required. The peak respiratory depressant effect lasts longer than the peak therapeutic effect; extra caution when dosing is recommended.

The naltrexone component of morphine sulfate ER/naltrexone (Embeda) is formulated such that, if the capsule is swallowed whole or opened and sprinkled over applesauce, the morphine component will be released while the naltrexone will remain sequestered in a film coating that is resistant to digestion. However, if the capsule contents are chewed or crushed, the naltrexone is released, reversing the effects of the morphine, thus reducing the likelihood that the product will be abused by disabling the extended-release mechanism. No studies have established whether this hypothesized reduction of morphine effects following chewing or crushing were clinically significant; the product labeling states that there is no evidence that the naltrexone in Embeda reduces the abuse liability.

Patients receiving other oxycodone products may convert on the basis of administering one-half of the current daily dose every 12 hours with oxycodone ER (Xtampza ER). For other opioids, see prescribing information. A 9 mg dose of Xtampza ER is approximately equivalent to a 10 mg dose of other oxycodone HCl products (ratio of 9:10 for other doses as well).

Oxymorphone ER (Opana ER) should be given on an empty stomach at least one hour prior to or two hours after eating. Maximum serum concentration was increased by 50% when given with food. An *in vivo* study with oxymorphone ER showed that the maximum concentration increased 31% to 70%, on average, following concomitant administration with ethanol. Co-administration must be avoided.

Apply buprenorphine buccal film to the inside of the cheek. It will dissolve in approximately 30 minutes. Individual titration should be in increments of no more than 150 mcg every 12 hours and should not occur any sooner than every 4 days. Reduce dose (and titration increments) in half for patients with severe hepatic impairment or mucositis.

Apply buprenorphine transdermal patch (Butrans) to the upper outer arm, upper chest, upper back, or the side of the chest. Rotate application sites, waiting a minimum of 21 days before reapplying to the same skin site. Apply to a hairless or nearly hairless, dry skin site. Do not apply to irritated skin. Do not use soaps, lotions, oils, or alcohol on the skin before the patch is applied. If the buprenorphine transdermal patch falls off during the seven days dosing interval, dispose of the transdermal system properly and place a new patch on at a different skin site. During the dose titration, two patches can be used for a total max dose of 20 mcg.

Fentanyl transdermal patch (Duragesic) patch should be applied to the chest, back, flank, or upper arm on dry, intact, hairless skin. Do not use soaps, lotions, oils, or alcohol on the skin before the patch is applied. If the patch falls off before three days of use, discard and apply a new patch at a different skin site. In an effort to minimize the risk of accidental exposure to fentanyl patches, the FDA is requiring the manufacturer of Duragesic to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers.[172] The current ink color varies by strength and is not always easy to see. This change is intended to enable patients and caregivers to more easily find patches on patients' bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest. The manufacturers of generic fentanyl patches are being requested to make similar changes.

The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance to crushing or chewing.

Opioid Morphine Equivalent Conversions[173]

This table is intended to provide an estimate of overall opioid exposure; it should not be used for dosing determinations (e.g., converting a patient from one opioid to another). Conversion factors may vary based on individual pharmacokinetics and duration of use (e.g., opioid-naïve versus chronic dosing). The same conversion is used for immediate- and extended-release oral products with the same opioid component unless otherwise specified. This table includes medications that are not reviewed in this class review for reference purposes. Likewise, some medications are not included in this table due to limited data. See prescribing information for detailed recommendations, when available, for converting among formulations and active ingredients.

Opioid	MME Conversion Factor
buprenorphine transdermal*	12.6
buprenorphine tablet or film	10
butorphanol	7
codeine	0.15
dihydrocodeine	0.25
fentanyl buccal, SL tablet, or lozenge†	0.13
fentanyl film or oral spray†	0.18
fentanyl nasal spray†	0.16
fentanyl patch‡	7.2
hydrocodone	1
hydromorphone	4
levorphanol tartrate	11
meperidine	0.1
methadone	3
morphine	1
nalbuphine	1
opium	1
oxycodone hydrochloride§	1.5
oxymorphone	3
pentazocine	0.37
tapentadol	0.4
tramadol	0.1

* Based on total micrograms exposure over 24 hours and assumes 1 mg parental buprenorphine = 75 mg oral morphine (e.g., 5 mcg/hr patch = 63 MME over 7 days = 9 MME/day).

† Multiply conversion factor by the number of micrograms in the dose.

‡ Based on total micrograms exposure over 24 hours and assumes 1 mg parenteral fentanyl = 100 mg oral morphine (e.g., 25 mcg/hr patch = 180 MME over 3 days = 60 MME/day).

§ Strengths of oxycodone ER capsules (Xtampza ER) should be converted to the oxycodone HCl equivalent prior to calculation using a ratio of 9 mg Xtampza ER to 10 mg oxycodone HCl.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published comparative clinical studies with the following agents: buprenorphine (Belbuca), buprenorphine (Butrans), hydrocodone ER (Hysingla ER, Zohydro), hydromorphone ER (Exalgo), morphine sulfate ER/naltrexone (Embeda), oxycodone ER (Xtampza ER), tapentadol ER (Nucynta ER), and tramadol ER (Ultram ER, Conzip).[174,175,176,177,178,179,180,181,182,183,184,185,186,187]

The following agents have demonstrated abuse-deterrence in placebo-controlled and/or active-comparator studies, which is commonly measured by a measure of drug-liking using a visual analog scale (VAS), although other measurements have also been used: Embeda capsules, Hysingla ER tablets, OxyContin biconcave tablets, oxycodone ER (authorized generics of Oxycontin) tablets, and oxycodone ER (Xtampza ER) capsules.

methadone (Dolophine) versus morphine sulfate SR

A total of 103 patients with pain requiring initiation of strong opioids were randomly assigned to treatment with methadone 7.5 mg every 12 hours and 5 mg every 4 hours, as needed, or morphine 15 mg sustained release every 12 hours and 5 mg every 4 hours, as needed.[188] After 4 weeks, patients receiving methadone had more opioid-related discontinuations than those receiving morphine (22 versus 6%; p=0.019). The opioid escalation index at days 14 and 28 were similar between the 2 groups. More than three-fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8; at 4 weeks, the proportion of patients with a 20% or more reduction in pain was similar: 0.49 in the methadone group and 0.56 in the morphine group.

oxycodone controlled-release (OxyContin) versus oxycodone immediate release

A multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain.[189] Patients were being treated with fixed-combination opioid/nonopioid analgesics at study entry. Patients received oxycodone CR 30 mg every 12 hours or oxycodone IR 15 mg 4 times daily for 5 days. No titration or supplemental analgesic medications were permitted. The mean baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 for the oxycodone CR-treated group and 1.3 for the oxycodone IR group (p>0.05). The 5-day mean pain intensity was 1.4 and 1.1 for the CR and

IR groups, respectively (p>0.05). Discontinuation rates were equivalent (33%). There was no significant difference between treatment groups in the incidence of adverse events.

Cancer patients who required therapy for moderate to severe pain were randomized to oxycodone CR every 12 hours (n=81) or oxycodone IR 4 times daily (n=83) for 5 days in a multicenter, double-blind study.[190] Rescue medication was allowed. Pain intensity remained slight during the study, with mean oxycodone CR doses of 114 mg/day and mean oxycodone IR doses of 127 mg/day. Acceptability of therapy was fair to good with both treatments. Discontinuation rates for lack of acceptable pain control were 4% with oxycodone CR and 19% with oxycodone IR. Fewer adverse events were reported with oxycodone CR than with oxycodone IR (p=0.006).

oxymorphone ER (Opana ER) versus oxycodone CR (OxyContin)

A multicenter, randomized, double-blind, placebo- and active-controlled trial was conducted to compare the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone CR in patients with moderate to severe chronic low back pain requiring opioid therapy.[191] Patients (n=213) were randomized to receive oxymorphone ER (10 to 110 mg) or oxycodone CR (20 to 220 mg) every 12 hours during a seven- to 14-day dose-titration phase. Patients achieving effective analgesia at a stable opioid dose entered an 18-day double-blind treatment phase and either continued opioid therapy or received placebo. With stable dosing throughout the treatment phase, oxymorphone ER (79.4 mg/day) and oxycodone CR (155 mg/day) were superior to placebo for change from baseline in pain intensity as measured on a visual analog scale (p=0.0001). Adverse events for the active drugs were similar; the most frequently reported were constipation and sedation. Oxymorphone ER was equianalgesic to oxycodone CR at one-half the milligram daily dosage with comparable safety.

META-ANALYSES

A meta-analysis compared tapentadol ER and oxycodone/naloxone ER (not available) to oxycodone CR (3 trials of tapentadol ER versus oxycodone CR with or without a placebo group; n=3,105).[192] Compared to oxycodone CR, tapentadol ER resulted in a better risk ratio reduction for discontinuation due to adverse effects (RR, 0.526; 95% CI, 0.456 to 0.607), discontinuation due to nausea and vomiting (RR, 0.526; 95% CI, 0.471 to 0588), and constipation (RR, 0.609; 95% CI, 0.545 to 0.68).

A Cochrane review of opioids (immediate and extended release formulations) for chronic low back pain (15 trials; n=5,540), found that tramadol was more effective for pain control than placebo (standardized mean difference [SMD], -0.55; 95% CI, -0.66 to -0.44; 5 trials; n=1,378).[193] Transdermal buprenorphine had a small, but significant impact on pain control (SMD, -2.47; 95% CI, -2.69 to -2.25; 2 trials; n=653), and stronger opioids (morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol) were also superior to placebo for pain control (SMD, -0.43; 95% CI, -0.52 to -0.33; 6 trials; n=1,887).

A systematic review compared transdermal buprenorphine to transdermal fentanyl using 17 clinical trials, including trials for indirect comparison.[194] Transdermal fentanyl was associated with a greater risk of nausea (odds ratio [OR], 4.66; 95% CI, 1.07 to 20.39) and treatment discontinuations due to adverse effects compared to transdermal buprenorphine (OR, 5.94; 95% CI, 1.78 to 19.87). No differences were found in efficacy.

SUMMARY

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting. No clinical data exist that distinguish analgesic efficacy of any of these products from the others. Pain management must be individualized and patients who do not respond to one opioid may respond to another.

Full opioid agonists do not typically have a ceiling for their analgesic effectiveness but the dose is limited by their adverse effects. Morphine is the standard drug of comparison. Methadone (Dolophine) may provide an effective alternative in palliative care of most patients with cancer pain referred for poor pain control and/or adverse effects. It is also useful in the treatment of opioid dependence. Morphine sulfate has been available as a twice-daily sustained-release oral dosage form (MS Contin) for many years. A morphine controlled-release dosage form (Kadian) is available for once daily use. Hydrocodone bitartrate extended-release (Hysingla ER, Zohydro ER) is available without an acetaminophen component. Both Hysingla ER and a new formulation of Zohydro ER contain properties to limit abuse, but only Hysingla ER has met FDA abuse-deterrent requirements. Hysingla ER is dosed once every 24 hours, while Zohydro ER is taken every 12 hours. Hydromorphone ER (Exalgo) is available for a once-daily dosing. Morphine ER/naltrexone (Embeda) is a formulation of morphine that theoretically reduces abuse potential with the addition of naltrexone and dosed once daily.

Tapentadol ER (Nucynta ER) and tramadol ER (ConZip, Ultram ER) are centrally-acting oral analgesics that bind to mu-opioid receptors and inhibit norepinephrine re-uptake. The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance to crushing or chewing. Tapentadol ER is dosed twice daily, while tramadol ER is dosed once daily. In 2014, tramadol-containing products were given Schedule IV Controlled Substance status.

Like the controlled-release forms of morphine, oxycodone CR (OxyContin) allows for less frequent (12-hour) dosing of an opioid. Oxycodone CR has a significant potential for abuse and has been associated with increases in crime and deaths due to illicit use. However, all opioids can be abused and are subject to illicit use. Oxycodone CR has been reformulated to include a delivery system that causes a gummy substance when tablets are crushed; the effects of this redesign on illicit use have yet to be seen. A new formulation of oxycodone ER, Xtampza ER capsules, offers another twice-daily treatment option as an abuse-deterrent formulation.

Oxymorphone hydrochloride (Opana ER), an opioid agonist, is a metabolite of oxycodone, which is taken twice daily.

The following medications are available as abuse-deterrent formulations: Embeda capsules, Hysingla ER tablets, OxyContin tablets, oxycodone ER (authorized generics of Oxycontin) tablets, and oxycodone ER (Xtampza ER) capsules.

Two agents in this review provide analgesia via transdermal routes. Buprenorphine (Butrans), a partial opioid agonist, and fentanyl (Duragesic), a full agonist, are available as transdermal patches. Buprenorphine transdermal patch should be changed every 7 days, while a new fentanyl transdermal patch is recommended every 72 hours.

One agent provides a buccal route for analgesia, buprenorphine buccal (Belbuca), which is dosed twice daily.

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